Radio-adaptive regimen attenuates features of cellular senescence

Albert R. Davalos[1,2], Bridget Gengler[2], Steven M. Yannone[1], and Judith Campisi[1,2]

[1]Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Mailstop 84-171, Berkeley CA 94720; [2]Buck Institute for Age Research, 8001 Redwood Boulevard, Novato CA 94945

Recent work from several laboratories suggest that cells in a state of irreversible growth-arrest (senescence) can have long-lasting deleterious effects within tissues, and that the presence of these cells can drive both aging and cancer. Moreover, mounting data indicate that senescent cells exhibit a robust senescence associated secretory phenotype (SASP). Several of the factors secreted at senescence are known to promote inflammation, which may lead to age-related pathologies.

It has been hypothesized that low doses of ionizing radiation (IR) can protect cells and organisms from the loss of viability caused by a subsequent high dose (5 Gy) IR, a phenomenon known as radio-adaptation or radiation hormesis. We found that low levels of IR (10- 20 cGy) attenuate features of senescence induced with high dose IR (5 Gy). Particularly, we determined that human fibroblasts exposed to a low priming dose of 10 cGy exhibit a significant reduction in secretion of IL-6, a key component of the SASP. In addition, we found that a hormetic regimen blunts the effects of paraquat, a known reactive oxygen species (ROS) generator.

An important clue regarding how low dose IR might abrogate the senescence response is our finding that cells must undergo at least one S phase in order to experience the protective effects. S phase is often required to 'reset' chromatin organization. Indeed, we found that a major chromatin-associated protein, HMGB1, is actively exported from nuclei and secreted by senescent cells, and that low dose IR prevents high dose IR-induced HMGB1 nuclear export and secretion.

To test whether changes in chromatin drove the protective effect of a hormetic regimen, we exposed cells to Trichostatin A (TSA), a histone deacetylase and chloroquine which relaxes chromatin. Cells pretreated with TSA prior to a challenge dose exhibited increase growth compared to cells only exposed to a challenge dose. Furthermore, we detected reduction in senescence-associated β-galactosidase staining in cells cultured with TSA prior to challenge dose IR. Finally, we determined that fetal lung, but not foreskin, fibroblasts underwent modifications at histone 3 lysine 9 following exposure to 10 cGy and that this effect appeared to increase with multiple exposures of low dose IR.

Therefore, our findings have uncovered a novel connection between the biological effects of low dose radiation and the senescence response, and have demonstrated low dose irradiation may confer protection from endogenous factors that trigger age-related pathologies.